Editorial Commentary: Allogenic Dermal Fibroblasts in Collagen Matrix Scaffold Enhance Rotator Cuff Repair in an Animal Model

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Abstract: There has been a recent surge of interest on the use of biologic supplements to facilitate rotator cuff repair healing. Experimental evidence appears to support use of allogenic dermal fibroblasts (ADFs), either in the form of local injection or tenocytes embedded in collagen matrix scaffold, to enhance healing of a repaired rotator cuff tendon tear in an animal model. When compared with the ADFs, the platelet-rich plasma (PRP)-induced response seems to be limited in terms of the specific increases in local collagen 1 concentration, thus resulting in a bone-tendon healing response that is inferior in both biology and biomechanical behavior under the same laboratory conditions. While on the one hand, there is pilot data supporting use of dermal fibroblast in the clinical setting, thus reinforcing the animal study findings, on the other hand, we are also aware of the encouraging biologic changes that occurred in the retrieved acellular dermal matrix (ADM) allograft that was used for superior capsular reconstruction as a treatment of irreparable rotator cuff tears. In theory, ADFs locally instilled as an injection should further enhance the healing response compared to the ADM. However, this needs to be further studied to be able to be widely applicable clinically.

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Rhee, Kim, Park, Jeong, Han, Jeon, and Oh are to be commended for yet another well-performed basic science study investigating the effects of allogenic dermal fibroblasts (ADFs) and platelet-rich plasma (PRP) on tendon-to-bone healing in a rabbit model of chronic tear rotator cuffs entitled "Allogeneic Dermal Fibroblasts Improve Tendon-to-Bone Healing in a Rabbit Model of Chronic Rotator Cuff Tear Compared With Platelet-Rich Plasma".[1] At 4 weeks, COL1 and BMP-2 mRNA expression was higher in ADF (1.6 ± .8 and 1.0 ± .3, respectively) than PRP-injected shoulders (1.0 ± .3 and .6 ± .3; $P = .019$ and .013, respectively). Collagen continuity, orientation, and maturation of tendon-to-bone interface were better in the ADF Injection Group than in the PRP Injection Group ($P = .024$, .012, and .013, respectively) at 12 weeks, and the mean load-to-failure was 37.4 ± 6.2 N/kg and 24.4 ± 5.2 N/kg in Groups C and D, respectively ($P = .015$). These authors concluded that ADFs enhanced the rotator cuff healing better than PRP in the rabbit model with higher COL1 and BMP-2 expression, with better histologic and biomechanical findings.

Despite several advances in the arthroscopic rotator cuff repair techniques, literature has noted varying degrees of failure rates for larger tears.[2] Hence, there is a recent surge in interest in using biologic supplementation of some form to enhance tendon healing in patients after arthroscopic rotator cuff repair. The ideal biologic supplement and its method of application to strengthen rotator cuff repair still remains to be proven. There are several biologic agents, including platelet-rich plasma, concentrated bone marrow aspirate,[3] adipose-derived connective tissue progenitor cells dermal fibroblasts[4,5] and tenocytes[6] (allogenic versus autologous) that were considered.

Recent literature reports favored use of allogenic dermal fibroblasts (ADFs) that are delivered in the form of an injection to the rotator cuff repair site[4,5] or autologous tenocytes embedded in a collagen matrix scaffold,[6] which have been used as an augment in different animal experiments with encouraging findings. As per the present study findings,[1] when compared with the ADFs, the platelet-rich plasma (PRP)-induced response seems to be limited in terms

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of the specific increases in local collagen 1 concentration, thus resulting in a bone-tendon healing response that is inferior in both biology and biomechanical behavior under the same laboratory conditions.

I agree with the authors that the data from this study could be a transitional study to show the effectiveness of ADFs on the repaired tendon-to-bone healing of chronic rotator cuff tear in humans. Another recently published pilot study on human subjects by Joo Han Oh's group found that the autologous dermal fibroblast injections were safe and effective in enhancing the healing of torn rotator cuff repairs in the short term.[7] Deliberation between the use of allogenic to autologous dermal fibroblast tissue is an altogether different topic of discussion (keeping U.S. Food and Drug Administration restrictions in view).

While on one hand, there is pilot data supporting use of dermal fibroblasts in the clinical setting, thus reinforcing the animal study findings;[7] on the other hand, we are also aware of the encouraging biologic changes that occurred in the retrieved acellular dermal matrix (ADM) allograft that was used for superior capsular reconstruction as a treatment of irreparable rotator cuff tears.[8-10] In theory, dermal fibroblasts locally instilled as an injection or tenocytes in a scaffold should further enhance the healing response compared to the ADM. However, this remains to be further studied for it to be applicable clinically. While it is encouraging to see the existing evidence on biologic augmentation of cuff repair with dermal fibroblasts from the animal experiment studies and the pilot data on human subjects, much more progress is desired before wide acceptance into clinical application can be expected. At the outset, the present study findings highlight important basic science data that could potentially influence future surgical treatment methods and decision making in rotator cuff tear management.

References

1. Rhee R-M, Kim YH, Park JH, Jeong HJ, Han J, Jeon S, Oh JH. Allogeneic dermal fibroblasts improve tendon-to-bone healing in a rabbit model of chronic rotator cuff tear compared with platelet-rich plasma. *Arthroscopy* 2022;38:2118-2128.
2. Kukkonen J, Kauko T, Virolainen P, Äärimaa V. The effect of tear size on the treatment outcome of operatively treated rotator cuff tears. *Knee Surg Sports Traumatol Arthrosc* 2015;23:567-572.
3. Muench LN, Berthold DP, Kia C, et al. Nucleated cell count has negligible predictive value for the number of colony-forming units for connective tissue progenitor cells (stem cells) in bone marrow aspirate harvested from the proximal humerus during arthroscopic rotator cuff repair. *Arthroscopy* 2021;37:2043-2052.
4. Lee JH, Kim YH, Rhee SM, et al. Rotator cuff tendon healing using human dermal fibroblasts: Histological and biomechanical analyses in a rabbit model of chronic rotator cuff tears. *Am J Sports Med* 2021;49:3669-3679.
5. Kwon J, Kim YH, Rhee SM, et al. Effects of allogenic dermal fibroblasts on rotator cuff healing in a rabbit model of chronic tear. *Am J Sports Med* 2018;46:1901-1908.
6. Roßbach BP, Gülecyüz MF, Kempfert L, et al. Rotator cuff repair with autologous tenocytes and biodegradable collagen scaffold: A histological and biomechanical study in sheep. *Am J Sports Med* 2020;48:450-459.
7. Yoon JY, Park JH, Rhee SM, et al. Safety and efficacy of autologous dermal fibroblast injection to enhance healing after full-thickness rotator cuff repair: First-in-human pilot study. *Orthop J Sports Med* 2021;9:232596712110529.
8. Hartzler RU, Softic D, Qin X, Dorfman A, Adams CR, Burkhart SS. The histology of a healed superior capsular reconstruction dermal allograft: A case report. *Arthroscopy* 2019;35:2950-2958.
9. Altintas B, Scibetta AC, Storaci HW, Lacheta L, Anderson NL, Millett PJ. Biomechanical and histopathological analysis of a retrieved dermal allograft after superior capsule reconstruction: A case report. *Arthroscopy* 2019;35:2959-2965.
10. Lederman ES, McLean JB, Bormann KT, et al. Histologic case series of human acellular dermal matrix in superior capsule reconstruction. *J Shoulder Elbow Surg* 2021;30:2146-2155.